REMARKS

Claims 1-101 are currently pending in the present application. Claims 3, 4, 10, 15, 17-24, 27, 31, 34-45 and 51-101 are canceled without prejudice to Applicants' right, and Applicants specifically reserve the right, to prosecute the subject matter of these claims in a related application. Claims 5, 12 and 28 have been withdrawn by the Examiner as drawn to a non-elected species. Applicants reserve the right to rejoin these claims when a generic claim is allowed. Claims 46-49 have been withdrawn by the Examiner as allegedly drawn to a non-elected invention. Office Action, page 5. New claim 102 is added. Claims 1, 6, 9, 13, 14, 16, 25, 26, 28, 30, 32, 33 and 46 are amended herein. Support for these amendments, and for new claim 102, may be found in the specification at least at page 7, line 24 to page 8, line 32; page 9, lines 15-28; page 10, lines 12-27; page 15, line 29 to page 16, line 26; page 43, lines 4-8; page 48; page 53, line 30 to page 54, line 30; page 62, lines 18-24; page 63, lines 22-34; and in the Examples. After entry of the present Amendment, claims 1, 2, 6-9, 11, 13, 14, 16, 25, 26, 29, 30, 32, 33 and 46-49 will be pending.

Claims 46-49 Should Be Rejoined

The Examiner has withdrawn claims 46-49 from consideration because "the scope of claims 1-8 and 25-33 was narrowed by amendment (*i.e.*, the PDE4 inhibitor may not be a polypeptide, hormone, cytokine, or nucleic acid), but the scope of claims 46-49 was not similarly narrowed." Office Action at page 3. As such, the Examiner states, claims 46-49 are drawn to a non-elected invention. Applicants traverse.

Claims 1 and 25 were amended in the Preliminary Amendment of October 6, 2005 to remove negative limitations (*i.e.*, the compound is not a "peptide," "protein" or "oligonucleotide"). It is not possible for the deletion of a negative limitation to *narrow* the scope of a claim. Moreover, the claim, as originally filed, recited that the compound was not a "polypeptide" or "nucleic acid." Thus, the deletion of the three negative limitations did not change the scope of claims 1 and 25.

In any event, Applicants herein amend claims 1, 25 and 46 to recite a specific PDE4 inhibitor compound. Thus, the basis for the Examiner's withdrawal of claims 46-49 is moot. Applicants respectfully request that the Examiner rejoin and consider claims 46-49.

The Objections to The Specification

The Examiner has objected to the specification as incorporating essential material by reference. Office Action at page 6. The Examiner objects to the incorporation by reference of the "unpublished provisional applications" at page 1, lines 5-6. According to the Manual of Patent Examining Procedure ("M.P.E.P."), "[a]s a safeguard against the omission of a portion of a prior application for which . . . benefit is claimed under 35 U.S.C. 119(e) . . ., applicant may include a statement at the time of filing of the later application incorporating by reference the prior application." M.P.E.P. 608.01 (Eighth Edition Incorporating Revision No. 4) at page 600-95. Because the provisional applications referred to at page 1, lines 5-6 are applications of which the present application claims benefit, the incorporation by reference is proper. Applicants respectfully request that the Examiner withdraw the objection to the specification on this ground.

The Examiner has also objected to the incorporations by reference of foreign patent documents in the paragraph at page 44, line 18. Office Action at page 6. Applicants have amended the claims to recite a single specific compound that is not disclosed in the foreign patent documents. As such, the foreign patent documents constitute nonessential matter, and their incorporation by reference is appropriate. *See* 37 C.F.R. 1.57(d). Applicants respectfully request that the Examiner withdraw the objection to the specification on this ground.

The Examiner has also objected to the incorporations by reference of non-patent publications in the paragraph at page 45, line 11. Office Action at page 6. Applicants have amended the claims to recite a single specific compound that is not disclosed in the non-patent publications. As such, the non-patent publications constitute nonessential matter, and their incorporation by reference is appropriate. *See* 37 C.F.R. 1.57(d). Applicants respectfully request that the Examiner withdraw the objection to the specification on this ground.

The Examiner has also noted the use of various trademarks, and has suggested capitalizing the trademarks and providing generic terminology. Office Action at page 6. Applicants have capitalized trademarks and provided accompanying generic terminology.

Applicants submit herewith, under 37 C.F.R. 1.125(b), a substitute specification, in marked and clean versions, addressing each of the above items. No new matter is incorporated into the substitute specification.

The Rejections Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Enablement

Claims 1-9, 11, 13-16, 25-27 and 29-33 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly being non-enabled. While the Examiner acknowledges that the specification is enabling for methods of modulating certain aspects of proliferation and differentiation of mammalian stem or progenitor cells with certain PDE4 inhibitors, the Examiner contends that the specification is not enabling for the entire scope of the rejected claims. Office Action at page 7.

Without acquiescing to this contention, and solely to facilitate prosecution and speed allowance of the application, Applicants have amended independent claims 1, 25 and 46 to recite a particular PDE4 inhibitor, and to specify that the stem cell or progenitor cell is a hematopoietic stem cell or progenitor. Applicants assert that these amendments obviate the Examiner's concerns regarding the scope of the claims.

With respect to hematopoietic stem cells, Applicants note that the Examiner contends that hematopoietic stem cells from placenta could not have been used without undue experimentation because "[h]ematopoietic stem cells were discovered in the placenta after the instant invention was made," citing Mikkola *et al.* Office Action, page 9. Applicants respectfully point out that placental hematopoietic stem cells, and methods of collecting the stem cells, were described in U.S. Application Publication No. 2002/0123141 (corresponding to Application No. 10/004,942 ("the '942 application")), which is incorporated by reference into the present specification at page 24, lines 22-25). Thus, a person of skill in the art would be able to use a PDE4 inhibitor to modulate the differentiation or proliferation of a hematopoietic stem cell or hematopoietic progenitor cell without undue experimentation, even if placenta were to be used as a starting source.

Thus, for the reasons set forth here, Applicants respectfully request that the Examiner withdraw the rejection of the claims on this basis.

Written Description

Claims 1-9, 11, 13-16, 25-27 and 29-33 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action, pages 10-13. In particular, the Examiner states that the specification comprises an insufficient description of the genus of PDE4 inhibitors useful in the present invention. Office Action, page 11.

Without acquiescing to the Examiner's position, and solely to facilitate prosecution and speed allowance of the application, Applicants have amended independent claims 1, 25

and 46 such that the recited PDE4 inhibitor is a specific compound, or a salt, hydrate, solvate, clathrate, enantiomer, diastereomer, racemate, or mixture of stereoisomers of that compound. The specific compound, a SelCID®, is described in the specification at least at page 43, lines 4-14. This amendment obviates the Examiner's rejection, and, as such, Applicants respectfully request that the Examiner withdraw the rejection of the claims on this basis.

The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 1-9, 11, 13-16, 27 and 31-33 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite on different bases. Office Action, pages 13-17. Applicants traverse with respect to each basis.

The Examiner has rejected claim 1 as allegedly indefinite in that it is drawn to a method of "proliferating or differentiating" a stem cell, but requires contact of the cell for such time as "differentiation" of the cell is modulated. Office Action, page 13. Applicants have amended claim 1 to clarify that the contact is for such a time as "proliferation or differentiation" is modulated. Claim 1 as amended is, with respect to this basis for rejection, sufficiently clear. Claims 2-9, 11 and 13-16, which depend from claim 1, are thus also sufficiently clear on this basis.

The Examiner has rejected claim 2 in its recitation of "under suitable conditions". Office Action, page 13. Without acquiescing to the propriety of this rejection, Applicants have deleted this phrase from claim 2, thereby obviating the rejection.

The Examiner has rejected claim 2 as allegedly indefinite because the recitation of "wherein said cell differentiates into a hematopoietic cell" could be an effect of the method recited steps or an additional step, and requires clarification. Office Action, pages 13-14. The quoted phrase is one non-exclusive effect of the claimed method, and not an extra method step.

The Examiner further states that claim 2, in which the recited cell differentiates, is "confusing" in that it depends from claim 1. Office Action at page 14. Claim 1 as amended recites that the cell proliferates or differentiates; because these are presented as alternatives, claim 2 is compatible with claim 1.

The Examiner rejects claim 3 as allegedly indefinite because "it includes as species 'embryonic stem cells', 'placental stem cells', and 'cord blood stem cells.' It is not clear to what extent, if any, these terms overlap." Office Action, page 14. Applicants acknowledge that the Examiner interprets the term "placental stem cell" to be "a stem cell that is isolated from the placenta in any manner." Office Action at page 14. Without acquiescing to the

Examiner's position, and solely to further prosecution of the remaining claims, Applicants have canceled claim 3 without prejudice.

Applicants note, however, that the basis for the contention that these terms are potentially overlapping is incorrect. In particular, the Examiner states that the definition of placental stem cells in the specification includes various cells that may be isolated from the trophectoderm, which is part of the embryo, and, as such, the term "embryonic stem cell' encompasses "placental stem cell". Office Action at page 14. The trophectoderm, however, gives rise to the trophoblast, and is not, in fact, considered part of the embryo. In contrast, embryonic stem cells are understood by persons of skill in the art to be cells derived from the inner cell mass (ICM), which is distinct from the trophectoderm, and which goes on to yield the embryo. Moreover, the specification states that placental stem cells "may be collected from the isolated placenta once it has been exsanguinated and perfused for a period of time sufficient to remove residual cells." Page 11, lines 16-18. Thus, the term "placental stem cell" is also non-overlapping with the term "cord blood stem cells."

The Examiner has rejected claim 4 as allegedly indefinite in that it recites "selective cytokine inhibitory drug" without defining the same. Office Action, page 14. Claim 4 is no longer pending, thereby obviating this rejection.

The Examiner has rejected claim 6 as allegedly indefinite in that it requires contacting to be conducted "within a subject," which, the Examiner states, could be a "culture dish." Office Action at page 15. Applicants disagree that one of skill in the art would mistake the term "subject" to encompass a culture dish. However, in the interest of facilitating prosecution, Applicants have amended claim 6 to clarify that the contacting is conducted *in vivo*, thereby mooting the Examiner's rejection.

The Examiner has rejected claim 9 as allegedly indefinite in its recitation of "CD34+ progenitor cell", and requires clarification. Office Action at page 15. Without acquiescing to the propriety of this rejection, Applicants have amended claim 9 to delete the term "progenitor", thereby mooting the rejection.

The Examiner has rejected claim 11 as allegedly indefinite because "it is not clear whether the limitation 'wherein said cell differentiates into . . .'" is an effect of the steps of claim 1 or recites additional method steps, and requires clarification. Office Action at page 15. The recited phrase is clear as one non-exclusive effect of the method steps of claim 1.

The Examiner has rejected claim 13 as allegedly indefinite in that it requires the contacting of claim 9 be conducted "within a subject", which could, according to the Examiner, be a culture dish, and "does not point out any relationship between the subject of

claim 13 and the cell and molecules of claim 9." Office Action at page 15. Applicants disagree that one of skill in the art would mistake the term "subject" to encompass a culture dish. However, in the interest of facilitating prosecution, Applicants have amended claim 13 to clarify that the contacting is conducted *in vivo*, thereby mooting the Examiner's rejection.

The Examiner has rejected claim 14 as allegedly indefinite, largely on the same basis as the rejection of claim 13. Office Action at page 16. Applicants have amended claim 14 to recite that the contacting takes place within a mammalian subject, that is, *in vivo*. Claim 14, as amended, therefore excludes contacting in a culture dish. Moreover, the Examiner states that "it is not clear whether the transplanting step therein occurs before or after the contacting step of claims 9 and 13". Office Action, page 16. Claim 14 requires that the cell that is contacted with the compound is a cell that *has been* transplanted into a mammalian subject. The transplanting therefore takes place before the contacting. The cell is then contacted with the compound recited in claim 1. As such, the relationship between cell, compound and mammalian subject is sufficiently clear. Claim 14 is, therefore, sufficiently definite.

The Examiner has rejected claim 15 as allegedly indefinite in its recitation of "relative to a control." Office Action at page 16. As claim 15 is no longer pending, this rejection has been obviated.

The Examiner has rejected claim 27 as allegedly indefinite in its recitation of "selective cytokine inhibitory drug." Office Action at page 16. As claim 27 is no longer pending, this rejection has been obviated.

The Examiner has rejected claim 31 as allegedly indefinite "in that it requires that 'the differentiation' of claim 25 'is differentiation into a hematopoietic cell." Office Action at page 17. Applicants have amended claim 31 to recite that the cell is contacted with the recited compound for a time sufficient to modulate the stem cell's differentiation into a hematopoietic stem cell, clarifying the effect the compound has on the recited stem cell. Claim 31 as amended is, therefore, sufficiently definite. Claims 32 and 33, which depend from claim 31, are thus also sufficiently definite.

For the above reasons, Applicants believe that the claims as amended are sufficiently definite, and respectfully request that the Examiner withdraw the rejections of the claims on this basis.

The Rejections Under 35 U.S.C. 102(b) Should Be Withdrawn

Claims 1, 6-8, 25, 29 and 30 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Pittenger, U.S. Patent No. 5,827,740 ("Pittenger"), which, the Examiner contends, discloses the differentiation of human mesenchymal stem cells using methyl isobutylxanthine. Office Action, pages 17-18 According to the Examiner, methyl isobutylxanthine is a "general phosphodiesterase inhibitor." *Id.* at page 18. The claims, as amended, recite a compound not found in Pittenger. Thus, Pittenger does not anticipate the claims as amended. Applicants therefore respectfully request that the Examiner withdraw the rejections of these claims on this basis.

The Examiner has also rejected claims 1, 2, 6, 7, 9, 11, 13-15, 25, 29 and 31-33 under 35 U.S.C. 102(b) as allegedly anticipated by Gaspar Elsas *et al.*, *Br. J. Pharmacol.* 130:1362-1368 (2000) ("Gaspar"). Office Action, page 18. According to the Examiner, Gaspar discloses treating mouse bone marrow, which comprises CD34+ hematopoietic stem cells, with rolipram, a PDE4 inhibitor. *Id.* The claims, as amended, recite a compound not found in Gaspar. As such, Gaspar does not anticipate the claims as amended. Applicants therefore respectfully request that the Examiner withdraw the rejections of these claims on this basis.

The Examiner has also rejected claims 1, 2, 6-9, 11, 13-15, 25 and 29-33 under 35 U.S.C. 102(e) as being allegedly anticipated by Davis *et al.*, U.S. Application Publication No. 2003/0171306 ("Davis"), which, according to the Examiner, discloses treating CD34+ stem cells from bone marrow with rolipram. Office Action, pages 18-19. The claims, as amended, recite a compound not found in Davis. As such, Davis does not anticipate the claims as amended. Applicants therefore respectfully request that the Examiner withdraw the rejections of these claims on this basis.

The Provisional Double Patenting Rejections Should Be Withdrawn

The Examiner has provisionally rejected claims 1-3, 7-9, 11, 15, 16, 25, 26 and 29-33 for nonstatutory obviousness-type double patenting over claims 1-3, 7, 9-11, 13, 20, 21, 30, 31 and 34-38 of copending application no. 10/411,655 ("'655 application"), in view of Feldman, U.S. Patent No. 5,665,754 ("Feldman"). Office Action at pages 19-20. The Examiner bases the provisional rejection on the alleged teaching in Feldman that PDE4 inhibitors also inhibit the production of TNF-α, and that the methods and compositions of the '655 application involve TNF-α inhibitors.

As noted above, Applicants have amended independent claims 1 and 25 to recite a specific compound. This compound is not taught or suggested by the '655 application or by

Feldman. Thus, the combination of the '655 application and Feldman cannot render these claims, and the claims that depend from them, obvious. As such, Applicants respectfully request that the provisional obviousness-type double patenting rejection be withdrawn.

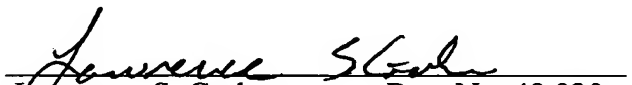
However, should the Examiner contend that the claims as amended are subject to a provisional obviousness-type double patenting rejection, Applicants respectfully request that such rejection be held in abeyance until either the current claims or the claims of the '655 application issue.

CONCLUSION

Applicants respectfully request that the present remarks be made of record in the file history of the present application. An early allowance of the application is earnestly requested. The Examiner is invited to contact the undersigned with any questions concerning the application.

Respectfully submitted,

Date May 15, 2006



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